# PATENT COOPERATION TREATY

# PCT

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
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| P045175PCT6 BSW/jdo | | |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
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| PCT/NL 03/00454 | 20.06.2003 | 20.06.2002 |

International Patent Classification (IPC) or both national classification and IPC

G01N33/68

Applicant

DE STAAT DER NEDERLANDEN, VERT.DOOR DE MIN.van vws

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 16.01.2004 | 16.11.2004 |

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 03/00454

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-23 as originally filed

**Claims, Numbers**

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-14 (RELATING TO SEQ ID 5-24) AND 1-12 (RELATING TO SEQ ID 3 AND 4) FOR IA

   because:

   ☒ the said international application, or the said claims Nos. 1-12 (RELATING TO SEQ ID 3 AND 4) FOR IA relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-14 (RELATING TO SEQ ID 5-24)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-14 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-14 |
| Industrial applicability (IA) | Yes: | Claims | 13-14 |
| | No: | Claims | |

2. Citations and explanations

   **see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. A search report was only established for those part of the claims, which relate to SEQ ID 3 and 4. Consequently, also examination will be restricted to the parts of **claims 1-14**, which relate to SEQ ID 3 and 4.

2. **Claims 1-12** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1: LEVELY M E ET AL: "IMMUNODOMINANT T-CELL EPITOPE ON THE F PROTEIN OF RESPIRATORY SYNCYTIAL VIRUS RECOGNIZED BY HUMAN LYMPHOCYTES" JOURNAL OF VIROLOGY, vol. 65, no. 7, 1991, pages 3789-3796

D2: TOBERY T W ET AL: "A simple and efficient method for the monitoring of antigen-specific T cell responses using peptide pool arrays in a modified ELISpot assay" JOURNAL OF IMMUNOLOGICAL METHODS, vol. 254, no. 1-2, 2001, pages 59-66

D3: MAECKER H T ET AL: "Use of overlapping peptide mixtures as antigens for cytokine flow cytometry" JOURNAL OF IMMUNOLOGICAL METHODS, vol. 255, no. 1-2, 2001, pages 27-40

D4: WYDE P R ET AL: "Respiratory syncytial virus (RSV) disease and prospects for its control" Antiviral Research, vol. 39, no. 2, 1998, pages 63-79

D5: SIDNEY J ET AL.: "Measurement of MHC/Peptide Interactions by Gel filtration", p 18.3.1 till 18.3.17 from "Current Protocols in Immunology" John Wiley & Sons (eds), 1999

D6 BUUS S ET AL: "Measurement of Peptide-MHC Interactions in Solution Using the Spin column Filtration assay", p 18.4.1. till 18.4.12 from "Current Protocols in Immunology" John Wiley & Sons (eds), 1999

The documents D4-D6 were not cited in the international search report. Copies of the documents are appended hereto.

**1. Novelty (Art. 33(2) PCT)**

**Claims 1-14**, relating to "ex vivo" MHC class II haplotype specific diagnosis of immune responses to and vaccination against human respiratory syncytial virus (H-RSV) are novel, when using peptides with SEQ ID 3 and 4, derived from the fusion protein (F protein) of H-RSV, since no document comprised in the state of the art, discloses said peptides to be MHC class II restricted T cell epitopes.

**2. Inventive step (Art. 33(3) PCT)**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-14 does not involve an inventive step in the sense of Article 33(3) PCT.

2.1. The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of **claims 1-14** does not involve an inventive step.
The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses a method for "ex vivo" MHC class II haplotype specific diagnosis of immune responses to H-RSV using T cell epitopes derived from H-RSV F protein. Determination of the HLA-restriction falls within the scope of the knowledge of a skilled person: It can be done by antibodies blocking binding of the peptides to the MHC molecules as exemplified in D1 or by binding assays as exemplified in D5 and D6, derived from a standard textbook in the art.
The subject-matter of claim 1 therefore differs from this known method in that peptides with sequences different from the ones provided in D1 are used for this purpose. The problem to be solved by the present invention is therefore regarded as providing methods for "ex vivo" MHC class II haplotype specific diagnosis of immune responses to H-RSV, using alternative T cell epitopes, derived from H-RSV F protein.
The solution to this problem, the provision of methods using T cell epitopes with SEQ 3 and 4 for this purpose, is not considered to involve an inventive step for the following reasons: The identification of new T cell epitopes, which can then be used for for "ex vivo" MHC class II haplotype specific diagnosis of immune responses to different antigens is state of the art (D2 and D3).

2.2. Dependent **claims 2-8** do not contain any features which, in combination with the

features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, the reasons being as follows:
The technical features of claims **2-4 and 7-8** are disclosed in D1 (p 3790, co 1, par 2 and fig.2).
The technical feature "measuring IFN gamma production (in an ELISPOT assay)" of **claims 5 and 6** is state of the art and described in detail in documents D2 and D3. The skilled person would therefore regard it as an obvious, alternative method to the one disclosed in D1, to use said assays in order to solve the problem posed.
Also the technical feature "to determine immune responses in vaccinated subjects" of **claim 9** is obvious to the person skilled in the art and for example mentioned in D2 (p 59, co 1).

2.3. **Claims 10-14**, relating to the use of said peptides for the production of a protective, haplotype specific vaccine and the evaluation of the protection of such a vaccine, seem to be obvious and not involve an inventive step, because T cell epitopes, derived by the methods of claims 1-8, have been suggested to be useful as such a vaccine (D1, abstract and p 3789, co 2, par 1, last sentence).

**3. Industrial applicability (Art. 33(4) PCT)**

**Claims 13-14** are industrially applicable.

For the assessment of the present **claims 1-12** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
The EPO does not allow a treatment step in a multi-step procedure.

**4. Clarity, support and disclosure (Art. 5 and 6 PCT)**

4.1. If the Applicant can overcome the objections, raised in 2.3. of the present communication, then **claims 10-14** are in contradiction to Art. 5 EPC.
In said claims the use of peptides with SEQ ID 3 to 4 in a protective vaccine is claimed, however, no example demonstrating the induction of a protective immune response induced by peptides with SEQ ID 3 to 4 is provided.

D4 (par 2.1. "Vaccines") lists some of the problems, encountered when trying to develop a protective H-RSV vaccine, and actually no protective H-RSV vaccine seems to be licensed up till now.
Claims 10-14 therefore seem to be an undue generalisation of the finding, that peptides with SEQ ID 3 and 4 are MHC class II restricted T cell epitopes and the proof, that they could form a potective vaccine is an undue burden for the person skilled in the art.

4.2. The following features render claims 1-9 unclear:
4.2.1. Claim 1, step (a) should be performed "in a sample of the subject" and step (b) seems to comprise the step of sample taking and is therefor in contradiction to the "ex vivo" nature of said claims. Even if the method of diagnosis is considered to be an "ex vivo" method, still step 1(b) suggests a treatment step.
4.2.2. The abbreviation (H-)RSV has no well recognized meaning and leads moreover to confusion, since it could also mean Rous-Sarcoma Virus. It should therefore be replaced by the full term.
4.2.3. According to Rule 6.2(a) PCT, claims shall not rely on references to the description. Therefore, the reference to Table 1 should be replaced by SEQ ID 3 and 4 and the MHC restriction.